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Review article

Neuroadaptations to antipsychotic drugs: Insights from pre-clinical and human *post-mortem* studies

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ABSTRACT

Antipsychotic drugs, all of which block the dopamine D2 receptor to a greater or lesser extent, are the mainstay for the pharmacological treatment of schizophrenia. Engaging in a deeper understanding of how antipsychotics act on the brain and body, at the cellular, molecular and physiological level is vital to comprehend both the beneficial and potentially harmful actions of these medications and stimulate development of novel therapeutics. To address this, we review recent advances in our understanding of neuroadaptations to antipsychotics, focusing on (1) treatment efficacy, (2) impact on brain volume and (3) evidence from human *post-mortem* studies that attempt to dissect neuropathological effects of antipsychotic drugs from organic schizophrenia neurobiology and (4) cardio-metabolic side effects. Our aim is to stimulate discussion on these highly clinically relevant topics and consider how we might use current and evolving knowledge and new methodologies in the fields of neuropharmacology and neuroscience, to advance our understanding of the long-term impact of antipsychotic treatment. Ultimately, this may inform the clinical use of these drugs.

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1. Prologue

Schizophrenia is a debilitating disease, ranked among the top 20 causes of disability worldwide (van Os and Kapur, 2009). The precise burden to society is difficult to estimate with precision, due to the diversity of data available and the manner in which it has been collected, nevertheless, large-scale studies examining indicators of the cost-of-illness generally suggest a disquieting picture of substantial human and economic costs. The lifetime prevalence of schizophrenia has been estimated at 0.25% in North America and 0.52% in Europe (Simeone et al., 2015). Indeed, in the European Union alone, a 2011 estimate suggested up to 5 million citizens suffer from schizophrenia and related psychoses (Wittchen et al., 2011). Schizophrenia is not purely a disease of mental health; patients have higher mortality rates and die 12–15 years (on average) earlier than the general population (Saha et al., 2007). It may surprise some then, that schizophrenia leads to more loss of life than several cancers and other physical illnesses (van Os and Kapur, 2009). Whilst many of these deaths reflect suicide, the primary reason for increased mortality is physical causes, including cardiovascular disease (Hennekens et al., 2005; Saha et al., 2007).

After diagnosis of schizophrenia, for which there is still no objective diagnostic test (Fond et al., 2015; Prata et al., 2014), the clinical management of this devastating disorder is very much grounded in the use of antipsychotic drugs (APD) (Kapur and Mamo, 2003), all of which act at dopamine D2 receptors. Unfortunately, these drugs do not effectively treat all symptom dimensions, particularly negative and cognitive symptoms. Furthermore they are associated with numerous side effects, decrease in efficacy over time, and a substantial proportion of patients fail to respond to multiple courses of APD, leaving a significant unmet medical need (Kapur and Mamo, 2003). Now more than 50 years since the introduction of these medications, little real progress has been made in advancing towards novel, non-dopaminergic therapeutics, despite decades of research effort and spending (Millan et al., 2015). In part, this reflects our emerging understanding of the complex, multi-factorial nature of schizophrenia pathophysiology, driven by advances in psychiatric genetics (Anon, 2014, 2015; Fromer et al., 2014), *post-mortem* brain tissue studies, and neuroimaging, particularly in prodromal individuals who have yet to transition to psychosis (Bloomfield et al., 2015; Crossley et al., 2015; Demjaha et al., 2014; Howes et al., 2015; Kambeitz et al., 2014; Selvaraj et al., 2014; van Erp et al., 2015). Combined, these approaches are beginning to paint a picture that schizophrenia is a complex syndrome, with likely multiple aetiologies and potentially distinct neurobiological phenotypes that may have profound implications for clinical treatment strategies. These insights will undoubtedly, in the fullness of time, provide the key pieces of information that will unlock novel drug treatments for schizophrenia, beyond dopamine and the D2 receptor.

On the other hand, such success is unlikely to be immediate. Given the medical need, there is another view, which suggests that engaging in a deeper understanding of how currently used APD act on the brain and the body, by dissecting their cellular, molecular and physiological effects in relevant model systems, is of paramount importance to speed the quest for new and improved medications. Such a systematic approach is likely to yield crucial insights into the mechanisms underlying the beneficial and potentially harmful effects of these drugs. This can provide logical routes to adjunct treatments, some of which, particularly anti-inflammatory drugs, are already showing encouraging signs of success in the clinic (Sommer et al., 2014). Furthermore, if one can better understand the cellular, molecular and physiological basis of the positive and negative effects of APDs, there is the potential to use rational drug design to develop novel antipsychotic agents that retain the beneficial effects, without the adverse ones (Cohen et al., 2013). In this review, we address this issue, by combining informa-

tion from different, but parallel, research lines, with a common goal – to understand at the cellular and molecular level, the effects of long-term APD treatment on the brain and body, which ultimately, may inform the clinical use of these drugs and the development of new APD. In doing so, we first briefly introduce the history of the development and current application of modern antipsychotics. We then present evidence from parallel lines of research into APD, focussing in particular on three key areas: (1) treatment efficacy and failure, (2) potential impact on brain structure and (3) metabolic side effects. We also review the evidence from human *post-mortem* studies to dissect neuropathological effects of antipsychotics from schizophrenia neurobiology. Our overall aim is to stimulate a critical discussion on these highly clinically relevant topics. In particular, we aim to inspire debate on how we might use current and evolving knowledge and new methodologies in the fields of neuropharmacology and neuroscience to advance our understanding of the long-term impact of APD treatment, which ultimately, may inform the clinical use of these drugs.

1.1. Clinical use of antipsychotic drugs for the treatment of schizophrenia: concerns and controversies

Antipsychotics remain the mainstay of pharmacological treatment of schizophrenia (Kapur and Mamo, 2003; Samara et al., 2014). These drugs are classified into First Generation Antipsychotics (FGA), also referred to as typical antipsychotics, of which haloperidol and chlorpromazine are the prototypical examples, and the newer Second Generation Antipsychotics (SGA), or atypical antipsychotics, examples of which include risperidone, olanzapine, quetiapine, ziprasidone, and most recently aripiprazole and brexpiprazole (sometimes referred to as Third Generation Antipsychotics). FGAs were discovered serendipitously in the 1950's and remain effective in the treatment of psychotic symptoms. However, based on initial optimism that SGA are more effective in improving negative and cognitive symptoms of schizophrenia, as well as their more favourable side effect profiles, these agents have largely supplanted the use of FGA in clinical practice and treatment guidelines. Without question, SGA are effective in treating positive symptoms and are associated with significantly less motor side effects. However, the initial promise of efficacy in other domains remains controversial (Leucht et al., 2013).

The use of APD has dramatically increased over the past decade and more than 50 million prescriptions are dispensed annually (Snyder and Murphy, 2008). Importantly, in addition to psychosis, antipsychotics are increasingly being prescribed for use, under certain circumstances, in the treatment of depression, bipolar disorder and behavioural sedation in autism spectrum disorder (ASD) (Domino and Swartz, 2008; Kaye et al., 2003). In addition, there is increasing “off-label” prescription for anxiety disorders, insomnia and behavioural sedation in dementia patients (Maher et al., 2011). This increasing use, particularly of SGA, assumes that these drugs have few long-term adverse effects or other clinical issues. However, it has long been known that FGA are associated with a higher prevalence of extra-pyramidal symptoms (EPS), including tardive dyskinesia and akathisia, resulting in cautious use clinically (Lerner et al., 2015). Whilst the newer SGA have a much lower EPS liability (Rummel-Kluge et al., 2012), they come with different risks and challenges for patients and physicians alike. In particular, these drugs are associated with a high incidence of metabolic side effects including weight gain, metabolic syndrome and elevated risk for type-II diabetes (Mitchell et al., 2013a,b). Moreover, in recent years increasing evidence has emerged from both clinical studies and basic research to suggest a link between the dose and duration of APD treatment and a progressive loss of grey matter, which if true, may have significant clinical implications (Vita et al., 2015). Aside from the adverse effects of these medications, another

prevailing issue of fundamental importance is that the therapeutic response to APD is not only mixed, but also may decline with time (Kane et al., 2013; Kishimoto et al., 2013; Leucht et al., 2013). A substantial proportion of schizophrenia patients (up to 40%) also do not respond to first-line standard APD treatment. These individuals, described as “treatment resistant” represent a significant area of unmet medical need (Remington et al., 2014). Taken together, it is clear that whilst APD remain the mainstay for pharmacological intervention in schizophrenia, their use is not without risk, suggesting a cost: benefit profile that requires careful clinical management. Moreover, the mechanisms underlying these phenomena and the clinical implications remain poorly understood.

Advances in neuropsychopharmacology, neuroscience and neuroimaging techniques have allowed us to probe deeper into the action of APD at the molecular, neuropsychological and systems level to reveal how the brain and peripheral systems adapt to APD treatment. In the following sections we synthesise from this evidence base, to which we have contributed as authors, the current state-of-the art regarding the effects of APD on brain and body systems relevant both to the beneficial and potentially harmful aspects of these medications. Specifically, we first consider neuroadaptations relevant to treatment efficacy, particularly considering the dogma that all antipsychotics have similar efficacy. Here we present for the first time a new correlative analysis to challenge this notion. Second, we consider the growing evidence for effects of antipsychotics on brain structure and function from both clinical and preclinical studies, and the possible implications of this effect. Motivated by a seminal review of the neuropathological effects of APD (Harrison, 1999a), we update the available evidence from human *post-mortem* studies as to what constitutes disease-specific effects and what may potentially represent medication confounds, a fundamental challenge in unravelling the neurobiology of schizophrenia. Finally, we turn to the long-known relationships between antipsychotics and metabolic disturbances, with a specific focus on insulin signalling.

1.2. Classifications of antipsychotic drugs and their clinical efficacy

The question of which antipsychotic drugs (APD) should be preferred for treatment of schizophrenia is controversial, largely because of the substantial costs of SGAs (Leucht et al., 2013). Meta-analytical evidence of clinical trial data regarding efficacy suggests that clozapine is significantly more effective than all other SGAs (Leucht et al., 2013). After which, amisulpride, olanzapine, and risperidone are significantly more effective than the other drugs apart from paliperidone and zotepine, although these effect sizes were small (Cohen's *d*; range 0.11–0.33) (Leucht et al., 2013). These data challenge the dogma that the efficacy of atypical APD is the same. Dominant and unifying theories along with experimental and clinical evidence suggests that the efficacy of APD (except for aripiprazole) strictly depends on blocking dopamine D2 receptors (Creese et al., 1976; Kapur et al., 2000; Seeman et al., 1976).

Yet, the binding affinity profile of APD is substantially different. Antipsychotics bind virtually all neurotransmitter receptors, to a greater or lesser extent (Lieberman et al., 2008). Traditionally, FGA are seen as having higher binding affinity towards D2 receptors compared to SGA, which instead show low affinity for D2 receptors (Creese et al., 1976; Kornhuber et al., 1989; Seeman et al., 1976). Others have alternatively argued, based on multivariate statistical analysis, that the main mechanistic difference between FGA and SGA is the relative binding affinity towards 5-HT_{2A} and D2 receptors (Meltzer et al., 1989). In fact, Meltzer et al. have shown that SGA, but not FGA, displayed higher binding affinity for 5-HT_{2A} than for D2 receptors, a pharmacological marker that is notably summarized as a 5-HT_{2A}/D2 ratio. Although the 5-HT_{2A}/D2 ratio

has been constructively criticized as to whether it is a clinically-relevant mechanism (Kapur and Seeman, 2001), the theory based on the 5HT_{2A}/D2 ratio is still considered central to discriminate FGA from SGA (Meltzer et al., 1989) and it is widely used to interpret *a priori* clinical outcomes of APD.

In the literature however there is little evidence of whether the 5-HT_{2A}/D2 ratio contributes to clinical outcomes, such as efficacy and/or side effects, for the newer SGA, in light of the latest meta-analytic data. A recent multiple-treatments meta-analysis has shown significant differences in several therapeutic parameters even within same drug categories (Leucht et al., 2013). This novel evidence thus sets up a number of new questions. For example, from a drug development stand point, what is the relationship between the 5-HT_{2A}/D2 ratio and clinical outcomes? Furthermore, is the 5-HT_{2A}/D2 ratio suitable to discriminate FGA from SGA? In an attempt to answer these questions, here we review the literature using a correlative analysis to unravel the potential relationships between the serotonergic mechanisms of APD, clinical outcomes and classifications.

Specifically, we have carried out a correlative analysis between 5-HT_{2A}/D2 ratio of SGA and FGA and their overall efficacy along with all-cause discontinuation as reported by (Leucht et al., 2013). According to the terminology used by Leucht et al. (Leucht et al., 2013), here we refer to overall efficacy as the mean overall change in symptoms (positive and negative – total score from baseline to endpoint – as detected by standard tests, see (Leucht et al., 2013). All-cause discontinuation instead refers to any factors that have led to treatment discontinuation (Leucht et al., 2013). This includes weight gain, the use of anti-parkinsonian medication as an index of extrapyramidal side effects, increases in prolactin levels, the presence of electrocardiographic abnormalities and sedative effects (Leucht et al., 2013). Our correlative analysis has also explored the relationship between 5-HT_{2A}/D2 ratio and extrapyramidal side effects separately from all-cause discontinuation. Additionally, the association between clinical effects and ability to stimulate cortical and subcortical serotonin release, as measured with microdialysis in pre-clinical models was examined. A recent review has already suggested the relevance of analysing antipsychotic-driven neurochemical output patterns (e.g. the serotonin pattern – defined as changes in the extracellular levels of serotonin), in pre-clinical models, to possibly predict clinical outcomes (Amato, 2015). In fact, it has been hypothesised that the symptoms of schizophrenia reflect unbalanced monoaminergic activity in cortical and subcortical areas (Carlsson et al., 1997), with antipsychotics improving symptoms by correcting this imbalance. It has also been speculated whether changes in serotonin release, as observed in animal models, could alone predict the clinical outcomes of SGAs. These additional mechanistic effects of APD are often underestimated. However, the powerful idea to study the neurochemical patterns of APD lies also in the perspective to investigate more complex mechanisms than mere receptor binding activity. In fact, it should be acknowledged that the neurochemical output driven by antipsychotics is not simply related to blocking receptors, given that neurotransmission depends on multiple complex mechanisms involving the complete synthesis, release and uptake machinery.

The following correlative analysis is focused on APD that were recently studied in a multiple-treatment meta-analysis comparing the efficacy and tolerability of SGAs plus chlorpromazine and haloperidol (Leucht et al., 2013). To make our analysis possible we used arithmetic means of receptor binding constants, obtained from at least two independent studies using both humans and animals. The necessity of using averaged receptor binding constant values is dictated by the heterogeneous figures attained by each of those studies. The serotonin neurotransmission pattern was obtained from pre-clinical studies, following acute APD treatment using microdialysis, as described in (Amato, 2015).

Table 1
Comparative correlations of antipsychotic drugs 5-HT_{2A}/D₂ Ki ratio and clinical outcomes.

Antipsychotic drugs	5-HT levels ^a (%baseline)	5-HT _{2A} ^b	D ₂ ^b	5-HT _{2A} /D ₂ Ki rank ^b	Clinical outcome ranks [*]		
					Overall efficacy	Side-effects	All-cause discontinuation
Olanzapine	72.86	2.8	28	0.1	3	1.0	0.46
Clozapine	61	5	16.67	0.3	1	0.3	0.46
Risperidone	172	0.2	0.5	0.4	4	2.09	0.53
Zotepine	127.5	9.8	19.6	0.5	6	3.01	0.69
Quetiapine	136	189.3	315.5	0.6	8	1.01	0.61
Asenapine	97.41 ^c	5.5	6.9	0.8	13	1.66	0.69
Lurasidone	82.17	2	1.7	1.2	14	2.46	0.77
Chlorpromazine	48	6.7	4.19	1.6	12	2.65	0.65
Aripiprazole	67.37	8.7	0.55	15.8	9	1.20	0.61
Haloperidol	49.71	52.4	1.64	31.9	7	4.76	0.8

Receptor binding constants (nM) are mean values from humans and rats [^b Refs. (Ichikawa et al., 2002; Ishibashi et al., 2010; Kroeze et al., 2003; Meltzer et al., 1989; Needham et al., 1996; Richelson and Souder, 2000; Richtand et al., 2007; Shahid et al., 2009; Werner et al., 2013)]. The 5-HT levels (%baseline) are mean values from rodents [^aRef. (Amato, 2015) and ^c Refs. (Bjorkholm et al., 2015; Franberg et al., 2009; Franberg et al., 2012)]. * Ref. (Leucht et al., 2013).

Table 2
Comparative correlations of antipsychotic drugs 5-HT_{2A} brain levels and clinical outcomes.

Antipsychotic drugs	5-HT _{2A} /D ₂ ^b	5-HT _{2A} ^b	D ₂ ^b	5-HT levels rank ^a (%baseline)	Clinical outcome ranks [*]		
					Overall efficacy	Side-effects	All-cause discontinuation
Risperidone	0.4	0.2	0.5	172.00	4	2.09	0.53
Quetiapine	0.6	189.3	315.5	136.00	8	1.01	0.61
Zotepine	0.5	9.8	19.6	127.50	6	3.01	0.69
Asenapine	0.8	5.5	6.9	97.41 ^c	13	1.66	0.69
Lurasidone	1.2	2	1.7	82.17	14	2.46	0.77
Olanzapine	0.1	2.8	28	72.86	3	1.0	0.46
Aripiprazole	15.8	8.7	0.55	67.37	9	1.20	0.61
Clozapine	0.3	5	16.67	61.00	1	0.3	0.46
Haloperidol	31.9	52.4	1.64	49.71	7	4.76	0.8
Chlorpromazine	1.6	6.7	4.19	48.00	12	2.65	0.65

The 5-HT levels (%baseline) are mean values from rodents [^aRef. (Amato, 2015) and ^c Refs. (Bjorkholm et al., 2015; Franberg et al., 2009; Franberg et al., 2012)]. Receptor binding constants (nM) are mean values from humans and rats [^b Refs. (Ichikawa et al., 2002; Ishibashi et al., 2010; Kroeze et al., 2003; Meltzer et al., 1989; Needham et al., 1996; Richelson and Souder, 2000; Richtand et al., 2007; Shahid et al., 2009; Werner et al., 2013)]. * Ref. (Leucht et al., 2013).

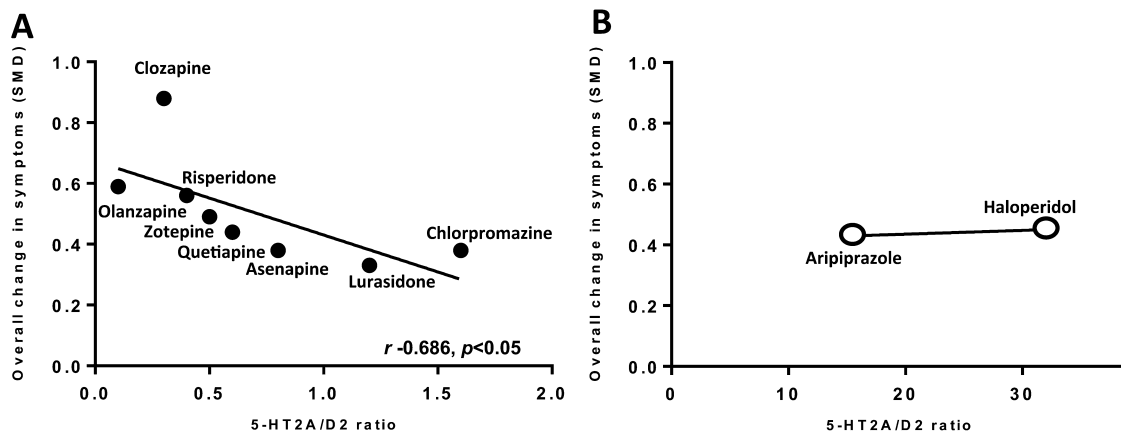


Fig. 1. Relationship between clinical efficacy of SGA and FGA drugs and their 5-HT_{2A}/D₂ ratio.

Our correlative analysis could only include 10 of the 15 antipsychotics examined by (Leucht et al., 2013), due to the lack of microdialysis studies investigating the serotonin neurotransmission profile of amisulpride, paliperidone, sertindole, ziprasidone and iloperidone (Amato, 2015). The general data used in the correlative analysis are reported in Tables 1 and 2. Regarding the use of the serotonin 5-HT_{2A}/D₂ ratio as a predictive factor for clinical outcomes, we found that this measure was significantly associated with the overall efficacy of most APD ($p < 0.05$), with the exceptions of aripiprazole and haloperidol (Fig. 1A, B). Since the latter antipsychotics skewed the representation of the data in all domains to the left, aripiprazole and haloperidol are plotted on an independent x-axis (Figs. 1B, 2B C). Furthermore, the 5-HT_{2A}/D₂ ratio significantly

predicted all-cause discontinuation ($p < 0.05$, Fig. 2D), but not extrapyramidal side effects ($p > 0.05$, Fig. 2A). Regarding the use of the serotonin levels (% of baseline) as a predictive factor for clinical outcomes, we found that serotonin levels were significantly associated with the overall efficacy of risperidone, quetiapine, zotepine, asenapine and lurasidone ($p < 0.01$, Fig. 3), but not with the overall efficacy of clozapine, olanzapine, haloperidol, aripiprazole and chlorpromazine ($p > 0.05$, Fig. 3 – empty dots). To highlight the marked relationship patterns among antipsychotics, they are plotted in the same axes (Fig. 3). Finally, serotonin levels significantly predicted all-cause discontinuation during risperidone, quetiapine, zotepine, asenapine or lurasidone treatment ($p < 0.01$, Fig. 4D)

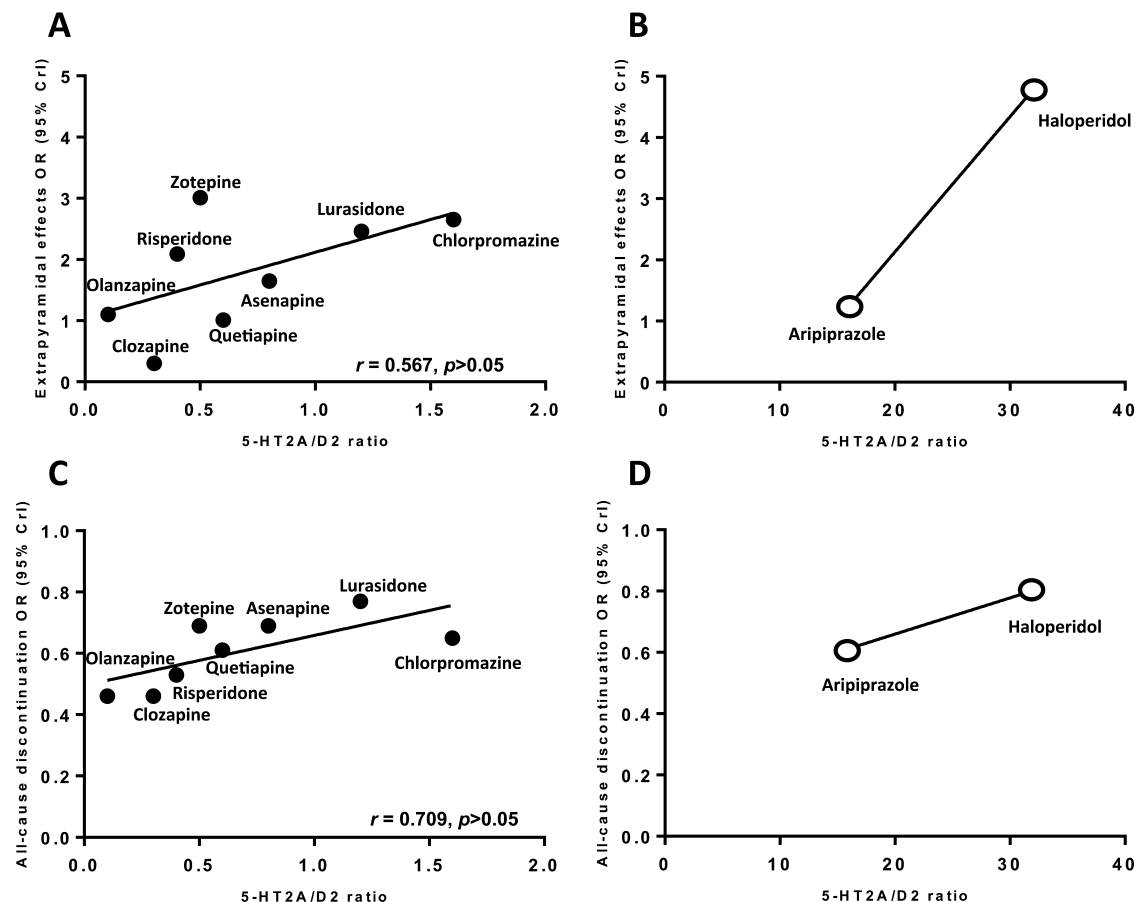


Fig. 2. Relationship between extrapyramidal effects (A, B) and all-cause discontinuation (C, D) observed during SGA and FGA drug treatment and their 5-HT2A/D2 ratio.

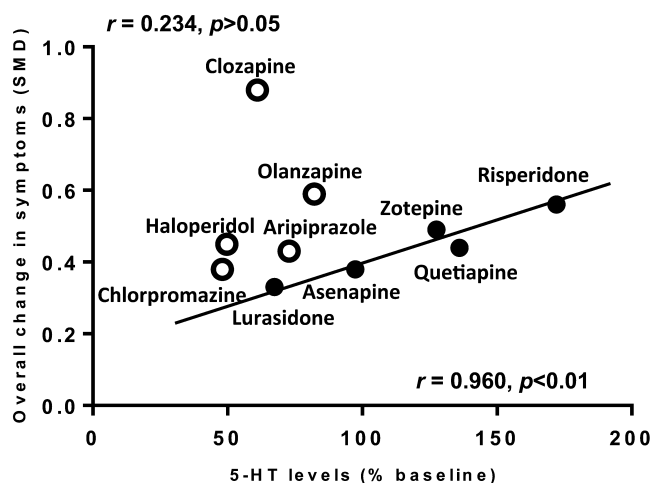


Fig. 3. Relationship between clinical efficacy of SGA and FGA drugs and their acute effects on extracellular 5-HT changes in the naïve rodent brain.

but not during clozapine, olanzapine, haloperidol, aripiprazole or chlorpromazine treatments ($p > 0.05$, Fig. 4C).

The results of this analysis therefore suggest that both the 5-HT2A/D2 ratio and the serotonin output are predictors of APD overall efficacy and of all-cause discontinuation (Figs. 1A, 2D, 3). A low 5-HT2A/D2 ratio was associated with the highest efficacy and with lowest discontinuation, while high serotonin levels were associated with highest efficacy and with the lowest discontinuation (see ranks in Table 2), although only within a sub-group of antipsychotics. The latter may suggest that the main action mech-

anism of subgroup of antipsychotics is expressed by stimulating serotonin release, which better links with their clinical outcome. It was previously observed that SGA and FGA have a different serotonergic binding and activity profile (Amato, 2015) that may be the underlying mechanism of the results of the present correlations. Perhaps a low affinity antagonism for 5-HT1A receptor associated with a high affinity antagonism/inverse agonism may be key for the role of serotonin pattern in clinical outcomes. Other compounds like clozapine, instead, show a high affinity partial agonism for 5-HT1A receptors and a high affinity antagonism for 5-HT2A receptor, which may maintain a low release of serotonin but promote dopamine release (Amato, 2015).

At first glance, it appears that the 5-HT2A/D2 ratio is therefore a better predictor of antipsychotic efficacy than the serotonin output criterion, as the latter was only able to predict the efficacy of a smaller number of compounds with a medium-to-low efficacy rank coefficient. Alternatively, the higher predictive power of the 5-HT2A/D2 ratio may also be seen as a consequence of its lower discrimination properties. In fact, all antipsychotics, except for haloperidol, aripiprazole and chlorpromazine displayed a low 5-HT2A/D2 coefficient; therefore the predictive power of the 5-HT2A/D2 ratio may reflect this greater number of compounds rather than selectivity *per se*. If this were the case, the ratio coefficient may not be suitable as either a mechanistic criterion to predict clinical outcomes, or as a criterion to classify antipsychotics as FGA or SGA.

The serotonin output pattern, while predicting the efficacy of only some antipsychotics may provide more accurate information on the relevance of neurochemical mechanisms. For example, it suggests that some antipsychotics are serotonergic and others

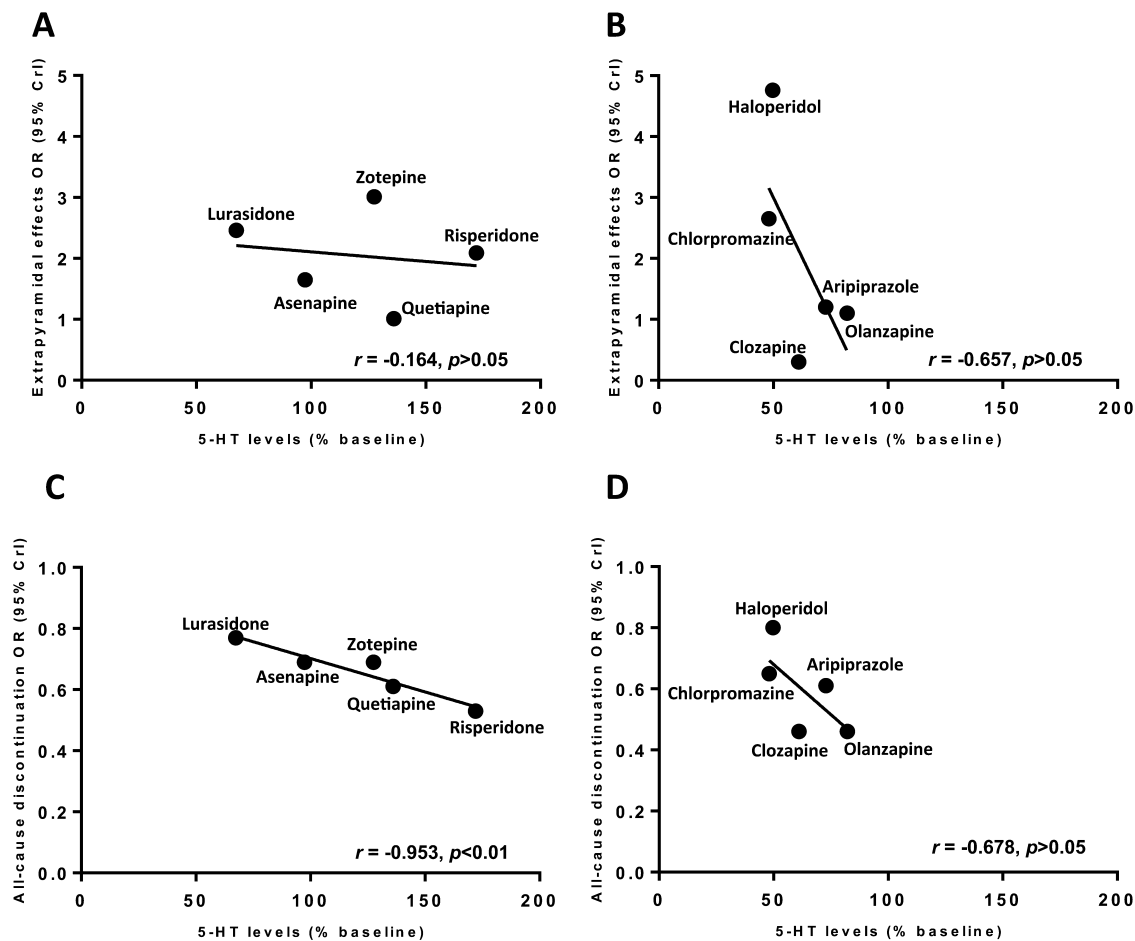


Fig. 4. Relationship between extrapyramidal effects (A, B) and all-cause discontinuation (C, D) observed during SGA and FGA drug treatment and their acute effects on extracellular 5-HT changes in the naïve rodent brain.

are not. In practice, the term “serotonin indirectly releasing agents” is more appropriate since these compounds facilitate the release of serotonin via agonism and antagonism of autoreceptors and/or postsynaptic receptors. Also, antipsychotics can affect the release of serotonin via other neurotransmitter systems summarized in (Amato, 2015).

Particularly, according to the present analysis, the newer SGAs, but not the traditional SGAs or FGAs, may be classified as serotonin releasing agents. While serotonin-releasing antipsychotics resulted in the present analysis to be overall less effective than the non-serotonin releasing agents, they are however associated with the lowest treatment discontinuation. Therefore, although the 5-HT_{2A}/D₂ ratio is a better predictor of efficacy than the serotonin output pattern, it appears to be a less selective classificatory criterion and poorly discriminates downstream effects of antipsychotics. Instead, the serotonin output pattern may provide a better classificatory criterion to define clinical outcomes for newer SGAs.

These new observations may be of relevance in disentangling and surpassing the commonly-held view of SGA and FGA mechanisms of action, which are currently based on receptor binding affinity. The systematic association of the clinical effects of antipsychotics with their neurotransmitter output patterns has the potential to generate a classification paradigm based on a neurotransmission domain (see Fig. 5 as an example). As such, the classification of antipsychotics as either serotonin or dopamine (or glutamate and so on) indirectly releasing agents may be a better predictor of clinical outcomes and treatment response. A limitation of the present analysis however is that we used the 5-HT level

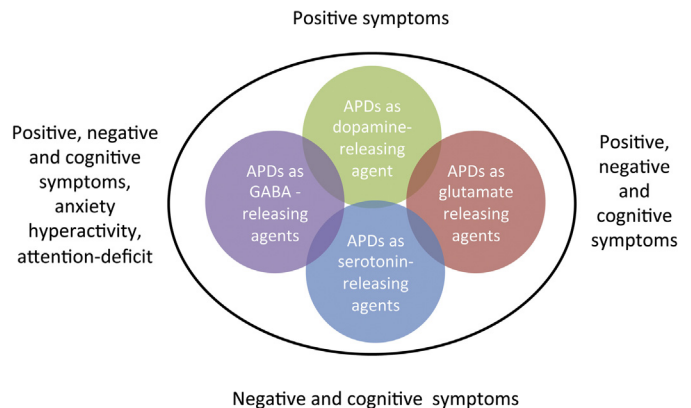


Fig. 5. A proposal for classifying antipsychotic drugs based on their modulation of a specific neurotransmitter domain in relation to different symptom clusters.

output following a single dose of antipsychotic, to compare with their clinical effects achieved using repeated and multiple doses of the same drugs. However, it should be noted that patients with schizophrenia often receive escalating doses of antipsychotic over their life time, thus partially mimicking the acute effects of the initial treatment. Further studies in pre-clinical models to assess the impact of chronic APD treatment on neurotransmitter levels, particularly serotonin, will help to clarify this.

To the best of our knowledge this is the first review analyzing the relationships between conventional APD mechanistic dogma

and clinical outcomes, as measured with multiple treatment meta-analysis. Furthermore, this is the first time that clinical outcomes are considered in relation to the serotonin output driven by APD, although the idea to relate antipsychotic efficacy with their effects on neurochemical release was previously advanced (Westerink, 2002).

1.3. Neuroadaptations to antipsychotic drugs

1.3.1. Impact of chronic antipsychotic drug treatment on brain morphology: a cause for concern?

Post-mortem and in vivo magnetic resonance imaging (MRI) studies have over the last four decades, contributed substantially to our understanding of the neurobiology and pathophysiology of schizophrenia. Post-mortem brains from schizophrenia patients show significant structural abnormalities (Andreasen et al., 1982a, 1982b, 1982c; Crow et al., 1989; Harrison, 1999b; Johnstone et al., 1976; Narr et al., 2005; Zipursky et al., 1998) with evidence for slight shrinkage (~5%) of the brain in terms of weight, length, and cortical volume (Gur et al., 1998a, 1998b; Johnstone et al., 1976) and for enlarged (~15%) ventricles (Cahn et al., 2002a; Cahn et al., 2002b; Crow et al., 1989; DeLisi et al., 1995; Gur et al., 1998a, 1998b; Johnstone et al., 1976; Lieberman et al., 2001). Advances in MRI acquisition and computational anatomy approaches have also revealed the presence of structural brain abnormalities in schizophrenia patients. Reductions in the volume of the whole-brain, temporal and frontal lobe grey matter volume and enlargement of the lateral ventricles are among the most replicated findings based on meta-analytical evidence (Ellison-Wright et al., 2008; Glahn et al., 2008; Haijma et al., 2013; Wright et al., 2000). Recently, the ENIGMA consortium reported the largest prospective meta-analysis of neuroimaging data from schizophrenia patients ($n=2028$) and controls ($n=2540$) to date (van Erp et al., 2015). Using data from 15 different centres worldwide, the authors report evidence for reductions in the grey matter volume of the hippocampus (Cohen's $d = -0.46$), amygdala ($d = -0.31$), thalamus ($d = -0.31$), accumbens ($d = -0.25$) and intracranial volumes ($d = -0.12$), as well as larger pallidum ($d = +0.21$) and lateral ventricle volumes ($d = +0.37$) (van Erp et al., 2015).

These neuroanatomical abnormalities appear to be evident from the first episode of schizophrenia (Vita et al., 2006) and are suggested to be detectable before illness onset in prodromal/high-risk individuals (Cannon et al., 2015; Dazzan et al., 2012; Mechelli et al., 2011; Pantelis et al., 2003; Schobel et al., 2013), although the data are not completely equivocal in this respect (Haukvik et al., 2015; Roiz-Santianez et al., 2015; van Haren et al., 2007). Meta-analyses of longitudinal MRI studies, which have the advantage of comparing back to baseline states, provide evidence to suggest that these brain volume abnormalities in schizophrenia may be progressive, with whole-brain and cortical grey matter volumes decreasing and lateral ventricle volumes increasing over time both in first-episode and chronic schizophrenia patients (Fusar-Poli et al., 2013; Kempton et al., 2010; Olabi et al., 2011; Vita et al., 2012).

Nevertheless, important questions remaining concerning neuroanatomical changes in schizophrenia, as detected by MRI. The first concerns the potential contribution of APD to the above mentioned brain volume abnormalities. The second relates to whether these anatomical changes are progressive with time. Both topics are the subject of lively and intense debate (Van Haren et al., 2013; Zipursky et al., 2013). Importantly, the presence of brain structural and functional abnormalities prior to any medication exposure, as highlighted by data from studies mentioned above, clearly suggests that APD are not the sole cause of brain volume changes in schizophrenia patients. Nevertheless, in the last two decades, increasing evidence has come to light to support the fact that APD exposure may well contribute to some of the neuroanatom-

ical abnormalities in schizophrenia patients. While the data are not unequivocal (Lewis, 2009; Weinberger and McClure, 2002), the increasing use of antipsychotics, particularly off-label prescribing, makes it critical that this issue is examined rigorously.

The largest meta-analysis of cross-sectional MR imaging studies on schizophrenia performed to date with data from over ~18,000 subjects (Haijma et al., 2013) indicates that reductions in whole-brain grey matter volume are associated with the dose of antipsychotics taken at the time of scanning. Data from longitudinal MRI investigations however, have the potential to provide the most compelling evidence for these potential medication effects, particularly if the assessment is carried out after the first episode of psychosis (FEP) and captures subsequent exposure to APD. Synthesising the evidence from such studies suggests that long-term exposure to APD is associated with sub-cortical grey matter volume enlargement, particularly in the caudate-putamen and pallidum and the loss of cortical grey matter volume (Cahn et al., 2002b; Gur et al., 1998a; Lieberman et al., 2005b; Thompson et al., 2009; Wood et al., 2001) and thickness (van Haren et al., 2011), supported by three systematic reviews on the subject (Moncrieff and Leo, 2010; Navari and Dazzan, 2009; Smieskova et al., 2009). The largest longitudinal study to date investigated the trajectory of brain volume changes in FEP patients ($n=211$) soon after illness onset, yielding a total of 674 high-resolution magnetic resonance scans. On average, each patient had 3 scans (≥ 2 and as many as 5) over 7.2 years (up to 14 years) (Ho et al., 2011). Data from this study and a follow up investigation of the same sample (Andreasen et al., 2013) confirmed that decreases in whole brain and regional grey and white matter volumes were significantly associated with higher exposure to APD. Notably, these findings remained significant after controlling for illness duration, illness severity, and substance abuse (Ho et al., 2011).

These findings are supported by recent meta-analysis of data from longitudinal MRI studies, which suggests a significant correlation between cumulative APD intake during the inter-scan interval and decreases in whole brain grey matter (Fusar-Poli et al., 2013). Similarly, activation likelihood estimation meta-analysis of voxel-based anatomical MRI data suggests brain regions that may be specifically affected following antipsychotic treatment in schizophrenia patients. These include relative volumetric decreases in the anterior cingulate and insular cortices (Radua et al., 2012), left lateral temporal cortex, left inferior frontal gyrus, superior frontal gyrus and right rectal gyrus (Torres et al., 2013). In contrast with prior results (Radua et al., 2012), areas of relative volumetric increase have also been identified in the left dorsal anterior cingulate cortex, left ventral anterior cingulate cortex and right putamen (Torres et al., 2013). More recently, other longitudinal studies, particularly those from the North Finland Birth Cohort study (1966 sample), have provided additional evidence to suggest that the dose and duration of APD treatment may predict grey matter volume loss in schizophrenia patients (Guo et al., 2015; Veijola et al., 2014). On the other hand, it is important to note that there are longitudinal studies that have reported no association between cumulative antipsychotic exposure and progressive brain volume alterations in schizophrenia patients although in some cases, the sample sizes are typically small and the duration of follow up is variable across studies (DeLisi et al., 1995; Haukvik et al., 2015; Kubota et al., 2015; McClure et al., 2008; Roiz-Santianez et al., 2015; Velakoulis et al., 2006).

Despite the weight of available neuroimaging evidence strongly suggesting an effect of APD on brain volume, the lack of longitudinally followed untreated patients as a control means it remains unclear whether this outcome is the effect of illness progression or drug treatment. Furthermore, as MRI currently cannot visualise changes at the cellular level, none of the human studies are able to link the imaging changes to post-mortem findings and therefore

the relationship between imaging-related structural changes and *post-mortem* findings remains unclear (Harrison, 1999a,b). Moreover, an enduring debate remains concerning the potential for a differential impact of FGA and SGA on progressive loss of grey or white matter (Vita et al., 2015). For example, hypertrophy of the caudate-putamen has long been thought to predominate in patients treated principally with FGA. However, a recent systematic review and new evidence in which clozapine-treated subjects are excluded from the SGA group questions this assumption (Ebdrup et al., 2013; Jorgensen et al., 2015). Reports of altered hippocampal volume following APD treatment are also inconsistent. Data from the ENIGMA schizophrenia-working group in fact suggests that the degree of hippocampus volume shrinkage is greater in medication naïve schizophrenia patients as compared to medicated patients, most of which were receiving SGA (van Erp et al., 2015). In contrast, longitudinal studies of cortical grey matter volume and thickness in schizophrenia patients have consistently identified, different trajectories of volume or cortical thickness changes in those patients receiving SGA as compared to FGA (Ansell et al., 2015; Lieberman et al., 2005b; Thompson et al., 2009; van Haren et al., 2008; van Haren et al., 2007, 2011). In the Iowa Longitudinal study, patients were treated naturalistically, thus there were no direct comparisons of the different APD classes (Ho et al., 2011). A recent meta-analysis has added to this debate (Vita et al., 2015). Here, the authors reported the results of a subgroup meta-analysis of studies on schizophrenia patients treated with either FGA or SGA. This revealed a differential and contrasting moderating role of APD intake on cortical grey matter changes, with more progressive grey matter loss correlating with higher mean daily antipsychotic intake in patients treated with at least one FGA (Vita et al., 2015). In contrast, less progressive grey matter loss was observed with higher mean daily antipsychotic intake in patients treated only with SGA (Vita et al., 2015). Whilst subject to the limitations common to all meta-analyses, these data at least suggest a testable hypothesis for future work, but interpretation of the results remains speculative in the absence of a mechanistic explanation for any such difference between FGA and SGA.

A more recent development is the application of existing and emerging neuroimaging methods (PET, MRS, Multicomponent Relaxometry [MCR] and Diffusion Tensor Imaging [DTI]) to provide indirect evidence for neuroinflammation in schizophrenia patients, by targeting chemical, physical, and geometrical changes that occur during the neuroinflammatory cascade (Pasternak et al., 2016). Neuroinflammation represents a complicated cascade of biological processes, which result in subtle biological, chemical, and physical changes, all of which may influence MR imaging signals. As a result, none of the currently available MRI or PET methods can be said to be specific to neuroinflammation *per se*. The interpretation of these findings is therefore limited and very few neuroimaging studies have directly investigated the presence of neuroinflammation in schizophrenia patients. Based on the limited available evidence, it may however be stated that if neuroinflammation does occur in schizophrenia, it is likely to be subtle and may be present in the early stages of the disorder (Bloomfield et al., 2016; Filiou et al., 2014; Pasternak et al., 2016, 2015). However, the potential contribution of APD exposure on MRI and PET methods thought to be sensitive to inflammation remains unknown.

Addressing the potential contribution of APD to brain volume abnormalities, whether these anatomical changes are progressive with time, and their impact on neuroinflammation remains problematic in clinical cohorts for the aforementioned reasons. Therefore, pre-clinical studies, in relevant animal models, represent a powerful translational approach to address these knowledge gaps. However, animal studies generally focus on a single APD, with haloperidol being the prototypical example. More critically, and somewhat unfortunately, many animal studies use a dose of

antipsychotics that is 10-fold higher than the clinical dose with inappropriate pharmacokinetics (Harrison, 1999a; Kapur et al., 2003). An exception to this are the rigorous *post-mortem* studies conducted in non-human primates, which used clinic-like plasma levels and reported that chronic treatment (2.5 years) with either haloperidol or olanzapine led a ~10% reduction in total brain weight and grey/white matter volume as compared to vehicle, particularly in the frontal and parietal lobes (Dorph-Petersen et al., 2005). Follow-up *post-mortem* neuropathology studies revealed that the reductions in parietal lobe grey matter volume in these animals was due to a decrease in glial cells, with preservation of neuronal numbers (Konopaske et al., 2007). Specifically, chronic APD treatment led to a ~20% reduction in S100 β -immunopositive astrocytes and a non-significant reduction in oligodendrocytes (Konopaske et al., 2008). Intriguingly, across all three studies there were no significant differences between haloperidol and olanzapine, although the sample sizes were limited by the species used. However, these single time-point, cross-sectional, histopathological studies did not use whole-brain imaging methods, limiting cross-species comparison with clinical measurements.

To overcome these limitations, we have implemented a model in laboratory rats that combines serial *in vivo* MR imaging (to delineate the impact & its time course using clinically-comparable technology), corroborated by high-resolution *ex vivo* MRI and *post-mortem* histopathology (to identify the cellular basis) and the use of clinically relevant drug doses and combinations based on matching D2 receptor occupancy with a method of continuous delivery using osmotic minipumps (Kapur et al., 2003; Vernon et al., 2011). This approach has revealed that chronic (8 weeks) treatment with either haloperidol or olanzapine leads to significant reductions in whole-brain and cortical grey matter volume, confirmed *post-mortem* (Vernon et al., 2011) (Fig. 5). For haloperidol at least, these effects are distinct from those of other psychotropics such as lithium, are dose-dependent and are apparently reversible on drug withdrawal (Vernon et al., 2012). Using voxel-wise, operator-independent tensor-based morphometry (TBM) and cortical thickness measurements, the effects of haloperidol and olanzapine were localised, in the cortex at least, to the anterior cingulate and somatosensory cortices (Vernon et al., 2014). *Post-mortem* follow up studies of the anterior cingulate cortex (ACC) in these animals confirmed no loss of neurons, but failed to confirm the loss of S100 β -positive astrocytes highlighted from the primate studies (Vernon et al., 2014) (Fig. 6). The reasons behind this discrepancy remain unclear, but could reflect species differences (rats vs. primates), region-specific effects (frontal vs. parietal lobe) or differential duration of exposure, given recent evidence for time-dependent effects on glial cells in the cortex of antipsychotic exposed rats (Konopaske et al., 2013). Notably, macaque monkeys treated with APD for 6 months in fact showed increased glial density in the dorsolateral prefrontal cortex, with no change in cortical thickness (Selemon et al., 1999), although the doses of APD given to these animals might not wholly match clinic-like plasma levels (Konopaske et al., 2007). Extending these findings, we recently reported evidence for profound microglial activation in several regions of the rat brain following chronic haloperidol or olanzapine treatment (Cotel et al., 2015), (Fig. 6), which may have implications for contradictory findings regarding putative microglial activation in positron emission tomography (PET) studies of chronic, medicated schizophrenia patients (Bloomfield et al., 2015; Doorduyn et al., 2009; Kenk et al., 2015; Takano et al., 2010; van Berckel et al., 2008). It would also therefore be of interest to examine the effects of chronic antipsychotic exposure on other MRI and MRS methods thought to be sensitive to neuroinflammation such as DTI and free-water imaging (Pasternak et al., 2016, 2015) in this controlled rodent model.

In all these studies, we could not find statistically significant differences between the effects of haloperidol and olanzapine,

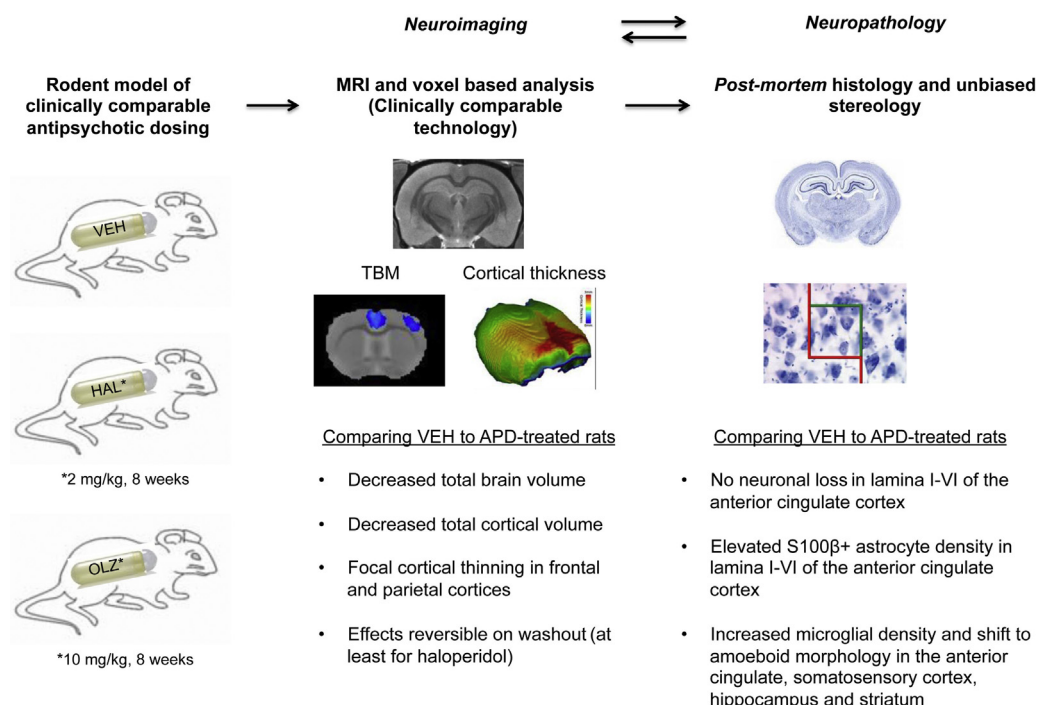


Fig. 6. Merging clinically comparable antipsychotic dosing and clinically comparable technology (MRI) reveals new insights into the effects of chronic antipsychotic dosing on brain volume, in particular the ability to link macroscale neuroimaging signal changes to their microscale cellular correlates.

although a full dose-response study may be beneficial in this respect. Further work is also required to fully delineate the cellular mechanisms underlying these neuroanatomical changes, which could reflect alterations in synaptic density, axon sprouting, fibre reorganization, myelin formation, glial cell density, or dendritic spines or arbours among others. Some support for the latter is evident again from primate studies in which APD exposure did not affect the density of axon terminals (Akil et al., 1999; Glantz and Lewis, 2001) but the density of dendritic spines and the extent of dendritic arborisation were decreased (Lidow et al., 2001). Interestingly, a recent rodent study makes the provocative suggestion that changes in dendritic spines at least partially contribute to neuroanatomical changes visualised using voxel-based morphometry analysis of anatomical MRI data (Keifer et al., 2015). Studies to unify these disparate findings are now underway in our laboratory, particularly between microglia and dendritic spine alterations given the provocative suggestion that microglia are critical mediators of activity-dependent synaptic remodelling and plasticity in the healthy brain (Kettenmann et al., 2013).

Although animal studies are inherently useful to dissect the effects of antipsychotics on brain structure, provided close attention is paid to dosing and pharmacokinetics, they are not without their limitations. In particular, it is important to stress that the majority of these data were collected from naïve animals, which do not capture the innate pathology of either schizophrenia or other psychotic disorders. Furthermore, because the mechanisms underlying these effects remain unknown, one should be cautious in drawing clinical inferences. Nonetheless, our studies provide a methodological and anatomical framework for future experiments to explicitly examine the relationships between changes in brain structure and activity, behavior and their *post-mortem* cellular correlates after chronic APD treatment, particularly comparing FGA and SGA. Clarification of these issues will provide important insights, which have the potential to aid the clinical management of schizophrenia and will allow a better understanding of the mechanisms underlying the progression of structural brain abnormalities in schizophrenia and the effects of antipsychotic medication on

such progression. Parallel human and animal studies may be particularly informative in this respect.

1.3.2. *Post-mortem studies of pre-synaptic and glial pathology: dissecting drug from disease effects*

Post-mortem brain tissue is undoubtedly a valuable tool in the search for the pathophysiology associated with schizophrenia. Furthermore, studies of *post-mortem* tissue may provide clues to the cellular and molecular effects of APDs in relevant clinical populations, negating some of the confounds of animal studies noted above. Given that schizophrenia subjects included within *post-mortem* brain cohorts have typically experienced a chronic disease course, the majority, if not all, will have been prescribed APD at some point in their lifetime (Harrison, 1999a,b). As discussed in the preceding section, it is now evident that antipsychotic medications can influence brain morphology with animal models implicating glial and synaptic/dendritic changes. (Cotel et al., 2015; Konopaske et al., 2013, 2007, 2008; Lidow et al., 2001; Vernon et al., 2014) In the following section of this review we will consider findings from *post-mortem* brain studies in schizophrenia, focussing on presynaptic and glial pathology, areas in which we have contributed to the literature and contemplate how APD exposure may influence these findings.

Several approaches have been used to assess effects of antipsychotics in *post-mortem* studies. First, measures may be compared between subjects on or off medications around the time of death. Disadvantages of this approach are that accurate determination requires access to toxicology measures, furthermore, even if a subject is not taking medications immediately prior to death, this does not take into account changes in brain morphology resulting from medication use over their lifetime (McCullumsmith et al., 2014). Moreover, depending on the cohort, the number of subjects off medications prior to death may be relatively small (Shan et al., 2013), or large (Barakauskas et al., 2010), thus limiting statistical power to detect an effect. A second approach is to assess the correlation between the measure/s of interest and lifetime antipsychotic dose, typically calculated as chlorpromazine or fluphenazine

equivalents. However, non-adherence to antipsychotic treatment is commonplace in individuals with schizophrenia (Cramer and Rosenheck, 1998). As such, estimates of lifetime antipsychotic dose are likely to be inaccurate. Furthermore, as discussed already, FGA and SGA may exert differential effects on brain tissue (Ansell et al., 2015; Vita et al., 2015), although this remains to be confirmed in experimental models using clinically comparable dosing (Dorph-Petersen et al., 2005; Vernon et al., 2014, 2012, 2011). This factor is difficult to tease apart in *post-mortem* studies, given that sample sizes are typically not powered to identify such an effect, and that subjects may have been prescribed both FGA and SGA over the course of their illness. A final, widely used, approach is to include complementary data from pre-clinical studies quantifying the measure/s of interest in animals, typically rodents or even primates, treated chronically with antipsychotics as detailed in the preceding section. However, this approach also has its challenges. The methodology utilized may not precisely mimic treatment course in humans, for example administration of antipsychotics for 21–28 days, the typical duration of such studies, probably does not adequately model a lifetime of treatment (McCullumsmith et al., 2014), while it should be remembered that drug half-life is much shorter in rodents (Kapur et al., 2003). Furthermore, investigation of antipsychotic effects are generally performed in healthy animals with no underlying pathology, thus context-dependent differences or drug x disease interactions have yet to be formally assessed in detail.

Evidence for pre-synaptic pathology in schizophrenia has emerged from electron microscopy studies (Kolomeets et al., 2005), although research in this area has most commonly involved quantification of proteins, or their associated transcripts, present in synaptic terminals. In particular, proteins associated with vesicle release at presynaptic sites, including synaptophysin, the soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) proteins SNAP-25, syntaxin, and synaptobrevin (VAMP), complexin I and II, synapsin and Rab3a, among others, have been used as proxies for synaptic density. Expression of these pre-synaptic markers has been explored *post-mortem* in schizophrenia, with decreased abundance reported in several brain regions including prefrontal cortex (Glantz and Lewis, 1997; Halim et al., 2003; Honer et al., 1999; Karson et al., 1999; Sawada et al., 2002; Beasley et al., 2006), hippocampus (Eastwood and Harrison, 1995; Fatemi et al., 2001; Harrison and Eastwood, 1998; Sawada et al., 2005; Thompson et al., 2003; Vawter et al., 2002; Young et al., 1998), thalamus (Blennow et al., 1996; Davidsson et al., 1999) and ventromedial caudate (Barakauskas et al., 2010). However, regional specificity may be implied given changes in presynaptic protein abundance were not reported in visual cortex (Glantz and Lewis, 1997; Thompson et al., 1998), visual association cortex (Beasley et al., 2005), orbitofrontal cortex (Ramos-Miguel et al., 2015), or nucleus accumbens (Barakauskas et al., 2010). Furthermore, decreased (Landen et al., 2002), unchanged (Barksdale et al., 2014; Eastwood and Harrison, 2001; Ramos-Miguel et al., 2015) and increased (Gabriel et al., 1997; Honer et al., 1997) levels of pre-synaptic proteins have been noted in the anterior cingulate region. Data from studies quantifying transcript expression are more difficult to interpret. While results from targeted investigations of pre-synaptic markers have found no consistent group differences (Fung et al., 2011; Glantz et al., 2000; Karson et al., 1999), several genome-wide microarray studies have identified enrichment of transcripts associated with synaptic function, including vesicle dynamics (Arion et al., 2007; Maycox et al., 2009; Mirnics et al., 2001; Mudge et al., 2008; Schmitt et al., 2012). Measures of pre-synaptic proteins are typically interpreted as reflecting synaptic density. However, alterations in synaptic size, vesicle number or vesicle release cannot be ruled out. Enhanced SNARE complex formation has been reported in several brain regions in schizophrenia

(Barakauskas et al., 2010; Honer et al., 2002; Ramos-Miguel et al., 2015) and may be suggestive of altered vesicle dynamics and synaptic dysfunction.

We suggest that the deficits in pre-synaptic markers detailed above are unlikely to be a consequence of antipsychotic use, based on multiple lines of evidence. Several studies have failed to identify significant correlations between lifetime antipsychotic dose and abundance of pre-synaptic proteins (Beasley et al., 2005; Gray et al., 2010; Halim et al., 2003), while comparisons between schizophrenia subjects prescribed APD immediately prior to death and those who were not indicate no difference in synaptic protein levels (Gabriel et al., 1997; Honer et al., 1997). Findings from pre-clinical studies examining pre-synaptic protein abundance in rodents are more mixed, although it should be noted that the majority of these studies have not used clinically comparable dosing (Kapur et al., 2003). Nevertheless, studies have either reported no effect of antipsychotics (Ramos-Miguel et al., 2015; Sawada et al., 2005), or increases in pre-synaptic protein levels in the hippocampus and cortex following APD administration (Barr et al., 2006; Scarr and Dean, 2012). Intriguingly, pre-synaptic protein and transcript expression is greater in the striatum following haloperidol administration (Barakauskas et al., 2010; Eastwood et al., 1994; Marin and Tolosa, 1997), consistent with the striatal hypertrophy induced by clinically comparable chronic haloperidol treatment in rats (Vernon et al., 2012) and with clinical MRI studies indicating increased striatal or pallidal volume in subjects with schizophrenia (van Erp et al., 2015). Overall, the evidence suggests that the predominant deficits in pre-synaptic proteins found in *post-mortem* studies are likely associated with the disease process rather than antipsychotic use, at least in cortical regions. This is further supported by recent findings from GWAS datasets, which heavily implicate synaptic genes and pathways in schizophrenia neurobiology (Anon, 2015; Fromer et al., 2014). However, a role for increased synaptic density, and/or changes in synaptic morphology, in antipsychotic-associated striatal hypertrophy is plausible (Konradi and Heckers, 2001).

The glial complement of the CNS is comprised of three major cell populations; oligodendrocytes, astrocytes and microglia. Oligodendrocytes are the major myelinating cells (Baumann and Pham-Dinh, 2001), astrocytes have been implicated in many essential CNS processes, including neurotransmission, glucose metabolism and regulation of blood flow, in addition to neuroprotection and response to injury (Sofroniew and Vinters, 2010), while microglia play an essential role in the brain's response to damage and may also act as a mediator of CNS synaptic plasticity (Tremblay, 2011). Dysfunction of all three glial populations has been implicated in the pathophysiology of schizophrenia (Trepanier et al., 2016).

Decreased oligodendrocyte density has been reported in pre-frontal grey matter in schizophrenia (Hof et al., 2003; Uranova et al., 2004; Vostrikov et al., 2007), however, in white matter, where the majority of oligodendrocytes are located, evidence for decreased oligodendrocyte density (Hof et al., 2003; Kerns et al., 2010) is outweighed by studies finding no significant change (Hercher et al., 2014; Mosebach et al., 2013; Segal et al., 2009; Uranova et al., 2004; Williams et al., 2013b). Quantification of myelin-associated proteins and associated transcripts has also produced mixed results. While global transcriptomic (Hakak et al., 2001; Katsel et al., 2005; Tkachev et al., 2003) and proteomic (Pennington et al., 2008) studies have identified changes in grey matter, and to a lesser degree white matter, in schizophrenia, the findings are not consistent with several targeted investigations of myelin protein or mRNA expression (Barley et al., 2009; Beasley et al., 2009, 2005; Hercher et al., 2014; McCullumsmith et al., 2007; Mitkus et al., 2008).

The effects of antipsychotics on oligodendrocytes and myelin are presently unclear. Bartzokis and colleagues proposed that antipsychotics, in particular SGAs, have a protective or myelin promoting effect (Bartzokis et al., 2009), however, *post-mortem* studies have

failed to provide evidence consistent with this theory. Comparisons of schizophrenia subjects on or off medication revealed no group differences in myelin transcripts (McCullumsmith et al., 2007), while several studies have reported a lack of significant correlation between antipsychotic dose and abundance of myelin proteins (Beasley et al., 2005; Hercher et al., 2014) or transcripts (Kerns et al., 2010; Mitkus et al., 2008). Conversely, we observed a negative correlation between lifetime antipsychotic dose and oligodendrocyte density in prefrontal white matter (Hercher et al., 2014). This is consistent with a study of the parietal cortex of rhesus monkeys following chronic antipsychotic exposure, which reported numerically reduced numbers of oligodendrocytes, although this failed to reach statistical significance (Konopaske et al., 2008). Corpus callosum volume, visualized on MR images, was also not significantly affected by chronic haloperidol or olanzapine treatment in rodents (Vernon et al., 2011), although, this does not preclude a decrease in oligodendrocytes, balanced by an increase in another cell type such as microglia, which may be altered in the white matter following treatment with the same drugs (Cotel et al., 2015). Further exploration of the effects of APD on white matter, oligodendrocytes and myelination are therefore warranted.

Contemporary *post-mortem* studies of astrocyte density in schizophrenia have typically utilized the marker glial fibrillary acidic protein (GFAP). Results to date have been somewhat inconsistent; lower density of GFAP-positive astrocytes have been reported in cortex in some studies (Rajkowska et al., 2002; Williams et al., 2013a), whilst others have failed to identify significant group differences (Arnold et al., 1996; Damadzic et al., 2001; Falkai et al., 1999; Radewicz et al., 2000). Of note, GFAP is expressed at relatively low levels in the protoplasmic astrocytes located in cerebral cortex, and is considered a more reliable marker of the fibrous astrocytes present in white matter (Middeldorp and Hol, 2011). While decreased astrocyte density has also been reported in white matter in schizophrenia (Williams et al., 2013a), this result is discrepant with two further studies that found no significant differences between groups (Falkai et al., 1999; Hercher et al., 2014), although it is worth mentioning that the latter study noted lower GFAP area fraction in schizophrenia, suggestive of altered astrocyte cell morphology or function. Overall, data from studies quantifying the density of GFAP-positive astrocytes are inconsistent with the presence of gliosis in this disorder. Having said that, cellular findings, alongside reports of regionally specific decreases (Johnston-Wilson et al., 2000; Katsel et al., 2011; Steffek et al., 2008; Toro et al., 2006; Webster et al., 2005), or increases (Barley et al., 2009; Feresten et al., 2013; Pennington et al., 2008; Rao et al., 2013; Toro et al., 2006) in GFAP or other astrocyte-associated protein or mRNA expression are potentially consistent with altered astrocyte function.

The impact of antipsychotics on astrocyte density or function remains to be elucidated, although current evidence suggests that exposure to APD may up-regulate astrocyte density or GFAP production. Positive relationships between GFAP levels and lifetime antipsychotic dose have been observed *post-mortem* (Barley et al., 2009; Toro et al., 2006), although others have reported no significant correlation between dose and GFAP-positive astrocyte density (Hercher et al., 2014) or protein abundance (Feresten et al., 2013; Pennington et al., 2008), or no effect of medication history on astrocyte-associated protein levels (Rao et al., 2013). Complementary pre-clinical studies in animals administered antipsychotics do not fully resolve this issue, Chronic APD treatment resulted in a reduction in S100 β -immunopositive astrocytes in macaques (Konopaske et al., 2008), however increased GFAP-positive astrocyte density was reported in rhesus monkeys administered FGA or SGA antipsychotics for six months (Selemon et al., 1999), whilst greater S100 β -positive astrocyte density was observed in the frontal cortex of rats (Vernon et al., 2014) following chronic antipsychotic treatment. In general, GFAP abundance appears to

be unchanged following haloperidol exposure in rats (Dean et al., 2006; Fatemi et al., 2008; Feresten et al., 2013; Steffek et al., 2008), although we found trends towards increased GFAP and aldehyde dehydrogenase L1 levels (Feresten et al., 2013). Clearly, further work using multiple astrocyte markers and different antipsychotics is required to clarify these effects.

Despite substantial recent interest in the role of inflammation in schizophrenia, conclusive evidence for the presence of inflammatory changes in the CNS remains elusive. Cellular investigations of microglial density have produced inconsistent results; while increased density of HLA-DR-positive microglia was reported in an early study (Radewicz et al., 2000), subsequent attempts to replicate this finding have revealed either no change (Hercher et al., 2014; Steiner et al., 2006), or subtle increases restricted to subpopulations of subjects (Fillman et al., 2013; Steiner et al., 2008). Reports of increased abundance of the microglial marker CD11b, or measures of putative microglial activation, such as pro-inflammatory cytokines or nuclear factor kappa B, in schizophrenia (Fillman et al., 2013; Paterson et al., 2006; Rao et al., 2013; Volk et al., 2015) provide some evidence for an inflammatory response, although divergent findings also exist (Dean et al., 2013; Fillman et al., 2014; Roussos et al., 2013).

While there is some evidence that antipsychotics may possess anti-inflammatory properties, these claims are often based on *in vitro*, non-clinical doses *in vivo*, or single doses of antipsychotics (Kato et al., 2011; Shin and Song, 2014; Venneti et al., 2006; Zhu et al., 2014). Indeed, *post-mortem* studies currently provide little credible evidence for either pro- or anti-inflammatory action of APD, noting no significant relationship between lifetime antipsychotic dose and density of activated or total microglia (Hercher et al., 2014; Radewicz et al., 2000; Steiner et al., 2008), and no association between medication history and expression of molecules associated with microglial activation (Rao et al., 2013; Volk et al., 2015). Furthermore, mRNA expression of pro-inflammatory cytokines is not altered in monkeys chronically exposed to haloperidol or olanzapine, although this study utilised whole tissue homogenates rather than microglial fractions (Volk et al., 2015). In contrast, recent evidence suggests that chronic treatment with both FGA and SGA may precipitate a shift towards reactive, amoeboid microglial morphology in rat brain (Cotel et al., 2015). However the consequences of this microglial activation and the functional state of these cells along the simplistic but widely used M1 (pro-inflammatory) and M2 (anti-inflammatory) polarisation remains to be clarified (Cotel et al., 2015). In addition, the relationship between antipsychotic exposure and expression levels of the translocator protein (TSPO) remain unclear. This is relevant since radio-ligands targeting TSPO are used as a clinical imaging index of putative microgliosis (Pasternak et al., 2016). Further studies are therefore warranted to dissect the relationships between chronic antipsychotic treatment and the immune system (Cotel et al., 2015). Overall, while *post-mortem* studies provide some evidence for lower oligodendrocytes and astrocyte density and increased microglial density, findings are equivocal. The role of APDs in glial pathology in schizophrenia remains subject to debate.

1.4. Metabolic side effects of antipsychotic drugs: the role of insulin signalling

Over the past 2 decades, the introduction of SGA has shed light on serious metabolic side-effects related to these agents, including weight gain, dyslipidemias, and glucose dysregulation diabetes (Allison et al., 1999a; Mackin, 2005; Nasrallah and Newcomer, 2004; Wirshing et al., 1998). The importance of gaining a better understanding of how these agents may be contributing to the metabolic burden that characterizes those with serious mental illness is highlighted by the observation that the leading

cause of death in this population is attributable to cardiovascular disease (CVD) (Hennekens et al., 2005). While there exists a differential metabolic liability between the various individual agents (with clozapine and olanzapine conferring the greatest metabolic risk) (Allison et al., 1999b; Lieberman et al., 2005a), it has become clear that no single agent is devoid of this risk. This observation is highlighted in first episode schizophrenia patients with little prior exposure to these medications (e.g. antipsychotic naïve) that have consistently been shown to be at increased risk for antipsychotic-induced metabolic adverse events (Correll et al., 2009; Patel et al., 2009; Perez-Iglesias et al., 2007; Zipursky et al., 2005). The implications of these observations are concerning and extend beyond cardiovascular health risks; in psychiatric populations medical comorbidity (including weight gain and diabetes) has been found to adversely affect medication compliance, self-esteem, quality of life, and functional outcomes (Adriano et al., 2012; De Hert et al., 2006a; Gold et al., 2007; Lyketsos et al., 2002). Moreover, obesity and glucose dysregulation have been linked to structural brain changes that may overlap with, and exacerbate, those characterizing schizophrenia (Adriano et al., 2012; Gold et al., 2007), although experimental evidence from rodent models is lacking.

Weight gain is a well-established risk factor for other cardiovascular morbidities including dyslipidemias, metabolic syndrome, and type 2 diabetes. In particular, as compared to the general population, patients with schizophrenia have a 3–5 fold increased prevalence rate of type 2 diabetes (De Hert et al., 2006b). However, the underlying etiology of this serious cardiovascular morbidity is not a straightforward phenomenon. Contributing effects include antipsychotic-induced weight gain (adiposity is a leading risk factor for type 2 diabetes), illness-related lifestyle factors (inactivity, high smoking rates, poor dietary habits), and a possible genetic predisposition to type 2 diabetes (Brown et al., 1999; Kohen, 2004; Mukherjee et al., 1989). Further adding to underlying complexity, APD have been shown to acutely, and directly impact molecular pathways of lipid and glucose metabolism.

It is now well accepted that APD can “directly” impair insulin sensitivity independently, and in addition to their weight gain propensities. Early evidence of this “direct” antipsychotic-induced phenomenon was supported by case reports of diabetic ketoacidosis in association with APD occurring even in the absence of weight gain (Guenette et al., 2013). Subsequent studies in patients on APD demonstrated that risk of glucose dysregulation could occur independently of indices of body weight (Henderson et al., 2005; Newcomer et al., 2002). However, to directly examine effects of these drugs on glucose metabolism avoiding any confounding effects of illness and weight gain, researchers also turned to the use of healthy/non-obese rodents, treated with acute doses of APD (avoiding early changes in adiposity). Indeed, work in rodents administered acute doses of an antipsychotic consistently demonstrate impairments in insulin sensitivity (hepatic and peripheral), and glucose tolerance (Albaugh et al., 2011, 2012; Boyda et al., 2010; Chintoh et al., 2009, 2008; Houseknecht et al., 2007; Martins et al., 2010). These perturbations appear to generally follow the metabolic liability observed in clinic (olanzapine, clozapine > risperidone > haloperidol), with early evidence also suggesting that newer SGA, considered to be more metabolically neutral (e.g. lurasidone) are also characterized by a degree of derangement in glucose homeostasis (Wu et al., 2013).

Emerging evidence also suggests that the direct effects of APD on glucose homeostasis can be modeled in humans. Analogous to what is seen in rodents, studies in healthy, normal weight volunteers, examining sub-acute (8–10 days) or acute (1–3 days) APD administration have shown early changes in glucose metabolism (Albaugh et al., 2011; Hahn et al., 2013a, 2013b; Sacher et al., 2008; Teff et al., 2013; Vidarsdottir et al., 2010a, 2010b). Interestingly, among those studies, Teff et al. suggested that even aripiprazole, an agent con-

sidered to be metabolically neutral, could induce early changes in insulin sensitivity (Teff et al., 2013). Thus, within the consideration that humans have greater physiological complexity and genetic heterogeneity than bred rodent strains, evidence suggests translational validity between these species in APD-associated glucose dysmetabolism. This observation in turn implies that rodent models of antipsychotic-induced glucose dysregulation may be useful to elucidate underlying mechanisms of these disturbances, including use of invasive techniques/tissue harvesting which are not feasible in humans.

The concept of brain-mediated regulation of glucose homeostasis emerged as early as the 1850's, with the demonstration that puncture of the 4th ventricle in rabbit's results in glycosuria. Today, it is well-established that peripheral hormones and nutrient signals communicate with the brain through respective central nervous system (CNS) receptors, resulting in preservation of energy and glucose homeostasis (Sandoval et al., 2008). The question thus emerges whether APD, which exert therapeutic mechanisms through the CNS, may also be causing metabolic perturbations through overlapping mechanisms. Indeed, many of the neurotransmitters and their respective receptors that are implicated in energy/glucose homeostasis, are impacted by APD (Nasrallah, 2008). As a starting point to disentangling potentially complex CNS-mediated mechanisms of antipsychotic-induced glucose dysregulation, it is first important to establish that APD impair glucose homeostasis through the brain. By employing stereotaxic techniques, it is possible to administer APD directly into specific brain regions and (precluding leakage into periphery) attribute any perturbations in glucose metabolism to CNS-mediated pathways. To our knowledge, three such studies exist (Girault et al., 2012; Hahn et al., 2014; Martins et al., 2010). Martins et al. administered a primed continuous infusion of olanzapine (330 µg total) during a hyperinsulinemic euglycemic clamp (HIEC), considered the gold standard to measure insulin sensitivity. They noted increased hepatic glucose production during hyperinsulinemia, suggesting that centrally mediated mechanisms may explain olanzapine-induced hepatic insulin resistance (Martins et al., 2010). Our own group examined a central bolus of olanzapine (75 µg total) during separate hyperglycemic clamps (to examine insulin secretion), and hyperinsulinemic euglycemic clamps (HIEC) (to examine peripheral and hepatic insulin sensitivity). Interestingly, in contrast to our work examining systemic, or peripheral olanzapine administration, intracerebroventricular (ICV) olanzapine administration failed to induce peripheral or hepatic insulin resistance, but replicated an impaired insulin response to glucose challenge. These data suggest that olanzapine-induced decrements in β -cell function could be mediated in part through CNS mechanisms (Hahn et al., 2014). A recent study similarly examined central administration of olanzapine during an HIEC (total dose 36 µg), failing to find effects on any parameters on insulin sensitivity (Girault et al., 2012; Martins et al., 2010). The reason behind observed discrepancies between studies is unknown, but might be explained by differences in dosing. Our work employed a quantitative method to establish ICV olanzapine dosing (i.e. inhibition of amphetamine-induced locomotion) (Hahn et al., 2014) where as the other groups used qualitative dose determination (observed sedative effects) (Girault et al., 2012). That said, as outlined in the preceding sections, D2 receptor brain occupancies remain the gold standard by which to establish therapeutic dose, and to our knowledge this has not yet been determined for ICV APD administration.

Addressing the limitations of currently available work to develop a model capable of dissecting contributing central effects of APD on glucose metabolism may have implications extending beyond understanding the underlying metabolic burden. As reviewed by others, the D2 receptor (central to our understanding of antipsychotic action) has been linked to CNS insulin signaling (Caravaggio et al., 2015; Girgis et al., 2008). Mounting evidence

suggests that insulin action in the brain exerts important regulatory functions on energy and glucose homeostasis (Filippi et al., 2012). Taken together, the possibility exists that APD therapeutic efficacy and metabolic side effects represent an overlapping phenomenon, possibly via CNS insulin signaling. Within the conceptualization of D2 antagonism as the common denominator for APD therapeutic efficacy, this hypothesized link fails to explain why antipsychotics with the greatest metabolic liability appear to have superior therapeutic efficacy (i.e. clozapine, and possibly olanzapine). However, the possibility exists that combinations of receptor synergisms or other poorly elucidated pathways (e.g. neuroinflammation) converge on pathways of therapeutic efficacy and metabolic deregulation. If this is true, future work in this area will be important to determine if it is possible to maximize therapeutic efficacy while targeting, or avoiding metabolic perturbations. Furthermore, early evidence might suggest that the answer to this question may be dependent on the specific domain of psychopathology under consideration. For example, in patients with schizophrenia, impaired glucose tolerance and decreased insulin sensitivity have been linked to decreased positive symptoms (Chen et al., 2013; Kirkpatrick et al., 2009) (Kirkpatrick et al., 2009; Zhang et al., 2015). Conversely, obesity and glucose dysregulation have been linked to cognitive deficits and brain volume loss (Adriano et al., 2012; Gold et al., 2007; van den Berg et al., 2009). Taken together, it is tempting to speculate that further investigation of mechanisms underlying antipsychotic-related metabolic side-effects, in particular glucose dysmetabolism, may be crucial to developing understanding of psychopathology, and interventions beyond current widely accepted models. Arguably, rodent models of antipsychotic-induced glucose dysregulation may hold a unique place in moving this field forward given their empirical practicality, and translational value to the clinic. Combination with neuroimaging to examine relationships between body fat (Mondelli et al., 2013), and brain structural and functional changes (Vernon et al., 2011) in relation to peripheral metabolic dysfunction may be of particular interest.

2. Conclusions

In this review, we integrate clinical and pre-clinical evidence from studies of antipsychotic efficacy, effects on neuroimaging signatures, metabolic side effects and *post-mortem* human brain tissue. A parsimonious synthesis of these parallel lines of research would suggest the following conclusions. First, in terms of antipsychotic efficacy, the serotonin output pattern of APD may offer an improved means of classification, compared to the 5-HT_{2A}/D₂ ratio for defining the mechanism of action of antipsychotics, particularly for newer SGA compounds and their likely clinical efficacy. Related to this, we present the first suggestion that clinical outcomes should be examined based on their relationship with the serotonin and other neurotransmitter output driven by different APD. This efficacy biomarker as defined here may be valuable to investigate the mechanisms of treatment failure. Second, there is now compelling evidence from both clinical and pre-clinical MRI studies that strongly suggests the dose and duration of APD treatment is associated with alterations in brain volume. Nevertheless, important questions remain unanswered. In particular the mechanism driving this effect and whether there are differential effects of FGA and SGA remain unknown and unqualified. More importantly, accepting that these changes do occur, the ultimate clinical consequences of antipsychotic-induced changes in brain volume remain unclear. While *post-mortem* brain studies in schizophrenia implicate alterations in synapses and glial cells, the potential impact, if any, of APDs on these findings remains to be determined, although evidence suggest that some features, particularly cortical

pre-synaptic changes, appear to be organic to the disease process. Finally, it has been long accepted that antipsychotics induce detrimental metabolic alterations, particularly SGA. Yet surprisingly little is still known about the mechanisms underlying these effects, how to obviate them and how they impact on brain structural and behavioral observations in patients.

A common vein running through these sections is the critical importance of utilizing animal models to dissect the precise effects of antipsychotics, on both the cellular and molecular level but also at a gross scale to link these to alterations in brain structure, function and behaviour. Provided close attention is paid to the use of clinically relevant dosing and effective use of clinically comparable technology (e.g. neuroimaging) such models have the potential to yield important insights, for example, the inter-relationships between metabolic abnormalities and brain function in addition to clarifying findings from *post-mortem* studies. An important omission, however, is that often these studies are done in naïve animals, in the absence of neuropathological changes relevant to schizophrenia. Whilst studies in naïve animals are crucial to begin to unravel APD effects, it is clear that the field now needs to move beyond this and begin systematic assessment of APD effects in relevant pathological model systems. Whilst this is a minefield in itself, as no animal model can recapitulate all features of this uniquely human disease, it may be possible using a reductionist approach to assess the impacts of antipsychotics on certain features. For example, chromosome 22q11.2 deletion syndrome is a neurogenetic disorder associated with high rates of schizophrenia and other psychiatric conditions (Schneider et al., 2014). A mouse model of the 22q11.2 deletion (Df(16)A(+/-)) shows remarkable anatomical overlap with human patients including alterations in cortico-cerebellar, cortico-striatal and cortico-limbic circuits (Ellegood et al., 2014). Such model therefore could provide a basis to test the effects of APD on brain volume alterations in a disease-specific context, although, many other such approaches may be visualized. Ultimately, we propose that gaining a deeper understanding of the effects of long-term APD treatment on the brain and body at the cellular and molecular level, may ultimately inform the clinical use of these drugs and, moreover, the development of new antipsychotic agents.

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